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EFFECTS OF LITHIUM CARBONATE ON PERFORMANCE AND BIOMEDICAL FUNC--ETC(U)
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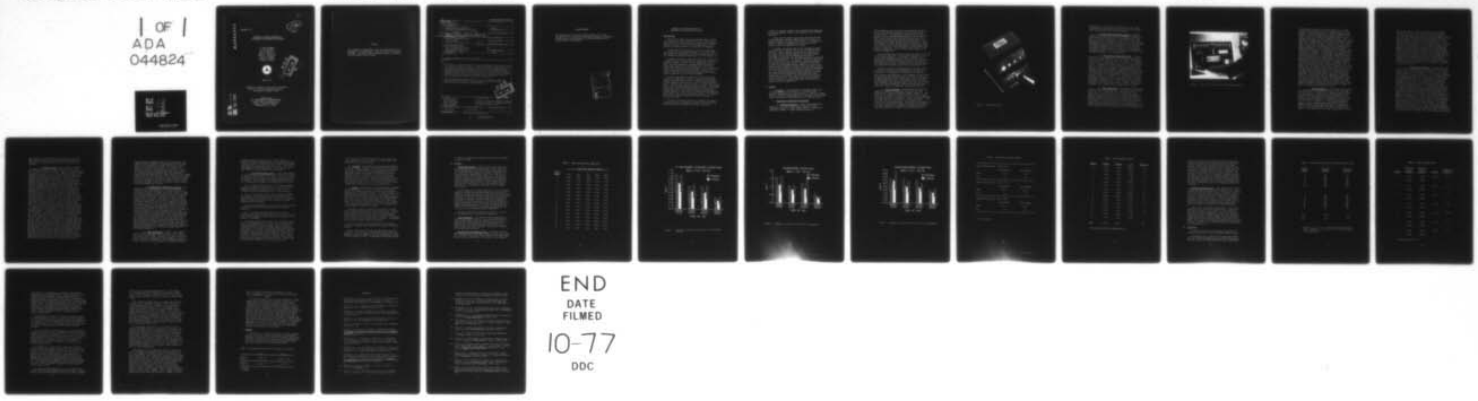

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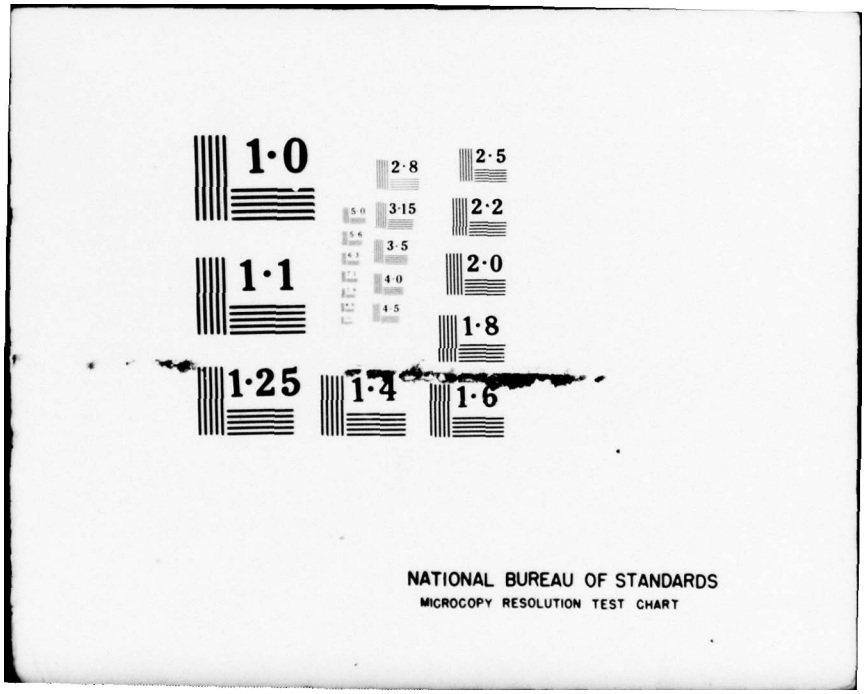
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16. Abstract

The effects of a single 600-mg dose of lithium carbonate were evaluated in a study of 15 healthy, normal male subjects. Subjects were studied, on two occasions, by utilizing a double-blind design--once receiving the lithium carbonate and once receiving a lactose placebo. Measurements were made of (i) complex performance, using the CAMI Multiple Task Performance Battery, (ii) hand steadiness, using the steadiness tester of the Motor Steadiness Kit, (iii) heart rate, (iv) the urinary excretion of 17-ketogenic steroids, epinephrine, and norepinephrine, and (v) short term memory, as measured by the Wechsler Memory Scale.

The only statistically significant effect due to the drug was for short term memory, in which scores made by subjects taking the placebo were higher than scores made by those taking the lithium carbonate.

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EFFECTS OF LITHIUM CARBONATE ON PERFORMANCE AND BIOMEDICAL FUNCTIONS

I. Introduction.

By 1970, the yearly output of published papers dealing with lithium had reached more than 250 (18). Not all of them dealt with the use of lithium in psychiatric treatment; however, this use of lithium is the major factor for the greatly increased interest in lithium and its compounds.

In 1949 lithium was reported by Cade (2) in Australia to be effective in treatment of mania. By the end of 1954, nine papers had been published in which lithium was used for treatment of mania with generally excellent results (16).

Although lithium was established by 1954 as an effective therapeutic agent for mania and its prophylactic effect to prevent recurrence of mania had been suggested, it was not until 1959 that Hartigan (9) suggested this prophylactic effect might apply to recurrent depression. It is now fairly well established that lithium does exert a prophylactic effect against both mania and depression. However, the status of lithium as an effective therapeutic acute medication for depression is still being evaluated.

An increasing number of airmen are being treated with lithium on a prophylactic basis. A number of these cases involve conditions other than the classical manic-depressive illness (bipolar) for which the use of lithium is now indicated. Some of these instances involve a history of an illness that is not otherwise grounds for medical denial. This brings up the issue of medical disqualification for the use of the medication itself. Prior to 1974, only two airmen using lithium appealed to the Federal Air Surgeon for certification, one in 1974, seven in 1975, and seven in 1976. It is anticipated that the use of lithium will increase markedly in the next few years.

The Office of Aviation Medicine, to explore its regulatory position, held a conference in April 1976 with leading aviation medicine consultants and experts on lithium.

A number of important opinions were expressed and significant conclusions reached. However, some questions still remained unanswered.

In July 1976 the Federal Air Surgeon requested that the Civil Aeromedical Institute (CAMI) look at the effects of lithium in respect to three specific areas: (i) subclinical effects on short term memory; (ii) visual motor skills (tremor); and (iii) cognitive functioning.

This paper will present some of the findings of experiments conducted at CAMI for the purpose of answering these questions. After planning conferences were conducted by Dr. Davis, chief of the Aeromedical Certification Branch, and members of the Aviation Physiology and Aviation Psychology Laboratories, the following conclusions concerning the study were reached: (i) the study should be limited to short term effects; (ii) performance, including measurements of cognitive functioning, would be evaluated by the CAMI Multiple Task Performance Battery (MTPB); (iii) short term memory would be assessed by using the Wechsler Memory Scale; (iv) hand tremor would be evaluated with the Motor Steadiness Test; (v) serum lithium levels would be measured by using the Atomic Absorption/Emission Spectrophotometer; (vi) the study should be of double-blind design with each subject serving as his own control; and (vii) Eskalith lithium carbonate would be used. The dosage would be 600 mg, which would be expected to produce peak serum lithium levels of between 0.5 and 0.6 mEq/liter.

II. Methods.

A. Subjects. Fifteen paid male volunteers, aged 19 to 27 years, served as test subjects. An interview and a physical examination were conducted prior to selection of each subject, and a full explanation of the procedures and a description of the nature of the medication to be used were given.

B. Apparatus and Measurement Techniques.

1. Biomedical Measures. Venous blood samples were drawn 2, 4, 6, 8, and 24 hours after ingestion of the appropriate capsules. These samples and an Instrumentation Laboratories Model 353 Atomic Absorption/Emission

Spectrophotometer with a nitrous oxide-acetylene operation in the flame emission mode were used to determine serum lithium levels. The calibration standard solution was an aqueous solution containing 0.864 mEq/liter of lithium, 140 mEq/liter of sodium, and 5 mEq/liter of potassium. The blank solution was the same solution without lithium, and a normal control serum was also used for validation. Blank and standard solutions, control serum, and sera to be tested were diluted 1:20 with deionized water. Serum samples were tested in duplicate. The instrument was calibrated to read directly in mEq/liter, and the results were rounded to the nearest 0.05 mEq/liter.

Urine specimens were collected from each subject 4, 8, and 12 hours after ingestion of the capsules and again at 0630 the following morning for an overnight specimen. These samples were preserved with boric acid and stored for later determination of their 17-ketogenic steroid, epinephrine, and norepinephrine values. The methods for these determinations have been reported earlier by this laboratory (11).

During the entire experimental period, the EKG's of the subjects were recorded on electromagnetic tape with chest electrodes in the CM_5 position connected to an Avionics Model 400 Electrocardiocorder. Three segments of the 24-hour recording were selected in a manner that would be expected to insure comparable levels of activity. Thus, for purposes of determining heart rate, 1 hour during each of the first two performance test sessions (1045 to 1145 and 1430 to 1530) and a 2-hour period while the subjects were asleep (2400 to 0200) were chosen for comparisons across drug conditions.

2. Motor Steadiness. Hand steadiness (tremor) was measured by using the steadiness tester from the Motor Steadiness Kit, Marietta Apparatus Company (Figure 1). The subjects were required to center the probe in each of five holes that decreased in size from 0.44 to 0.28 cm in diameter; the probe was 0.20 cm in diameter. Subjects attempted to keep the probe centered in each hole for 30 seconds with a 30-second rest between attempts. The subjects were required to use one hand only without support except for the forearm on the table. Subjects went through the sequence twice, each time starting with the largest hole and ending with the

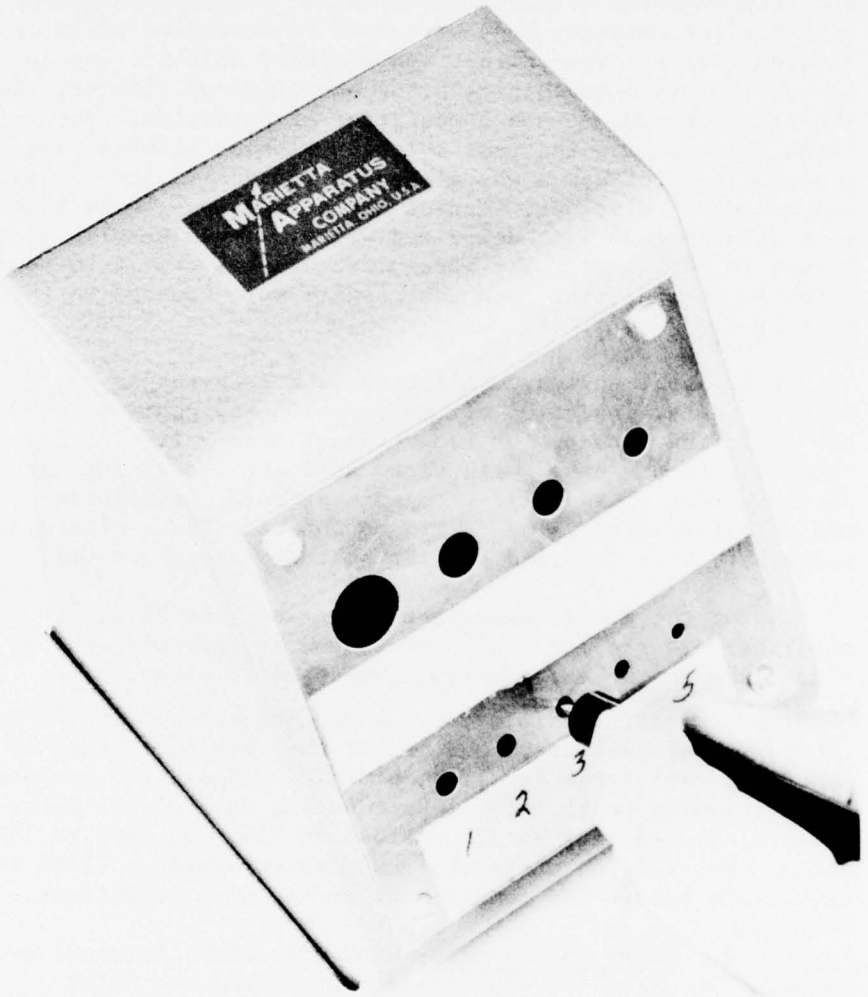

Figure 1. Steadiness tester.

smallest hole. The measure of steadiness was the number of contacts of the probe with the side of the hole accumulated (across holes) on an electric counter.

3. Multiple Task Performance Battery. The MTPB consists of six tasks that can be programmed independently across subjects and presented in any combination of from one to six tasks simultaneously. The MTPB system is computerized so that all signals, problems, etc., are presented automatically under computer program control and all scoring of times and accuracies is also automatic. The raw data are stored on magnetic tape for later, off-line analyses. The physical configuration of the tasks for a given subject is shown in Figure 2. Brief descriptions of the nature and performance demands of the tasks follow.

a. Red and green lights monitoring. At each corner and in the center of the subject's panel are located pairs of integral lights/switches. The upper light/switch in each case is red and the lower one is green. The normal state is for the green lights to be on and the red lights to be off. A signal on this task consists of a change of the state of a light and response is made by pushing the light/switch; this returns the light to its normal state and a computer record is generated that reflects the task involved, the subject, the time of onset (or offset) of the light, the time of response (or, if no response is made, the time of automatic return of the light to its normal state), whether a response was made, and which light was involved. The time from signal introduction to the occurrence of the response is measured in milliseconds. On the average, a signal (red or green) is introduced every minute. Signals that are not responded to are automatically removed after 15 seconds.

b. Meter monitoring. The displays for this task consist of four edge-reading meters having full-scale values of +50 and -50. A signal on this task consists of the deflection of one of the meters by a controllable amount either to the right or to the left of center, the zero point. Response is made by depression of one of the two buttons below each meter that is on the side toward which the meter had deflected. If a correct response is made, the signal is removed and the pointer returns to the zero (average) position when the button is released. The apparent difficulty of the task can be varied from very easy (i.e., a signal can

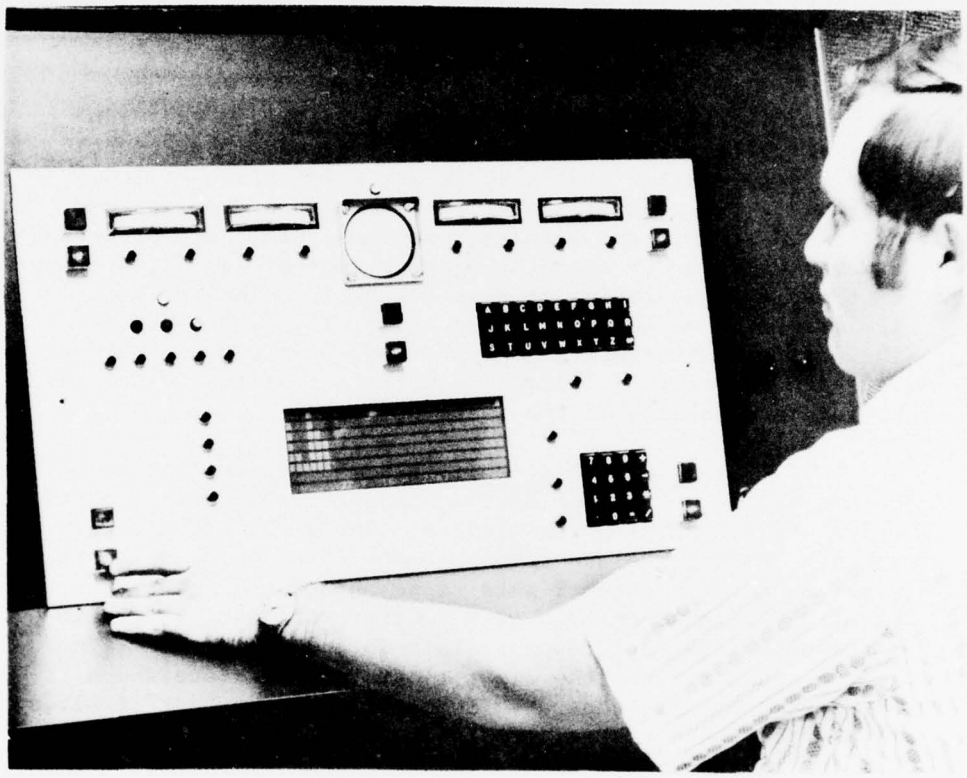

Figure 2. Console of the Multiple Task Performance Battery.

be detected at a glance) to very difficult (i.e., rather careful observation of the meter is required for 1 or more seconds) by the introduction of a "random" background disturbance. When the background disturbance (noise) is introduced, the pointer wanders about unpredictably with an average position of zero if no signal is present. With the addition of a signal, the pointer behavior continues as before but with an average position that has shifted either to the right or to the left of center. When a button for a given meter is depressed, the background noise is removed and the pointer stops on its "true" average value, thus giving immediate feedback as to the accuracy of the response. When the button is released, the background noise is again added to the pointer movement. In this study, the amplitude of a signal was set equal to the approximate maximum excursion of the pointer when driven by noise alone. Thus, fairly frequent readings beyond the normal maximum in either direction were clear evidence of the presence of a signal. Signals, introduced at an average rate of one each minute, were distributed unpredictably across displays and across time. A signal, when presented, remained until responded to or until replaced by a new signal. The response time for a given signal was computed in milliseconds on the basis of the time the signal was introduced; however, if the subject had not responded to the preceding signal, the time at which that signal was introduced was used in computing the response time to the later signal; this procedure was extended back in time to include all contiguous, not-responded-to signals in calculating the response time on this task. Thus, the number of signals presented in a given session was, for computational purposes, determined by the number of signals to which the subject had responded correctly.

c. Mental arithmetic. The display for this task is a 256-character (32 characters/row by 8 rows) Burroughs self-scan display. Characters are formed at a given character position by the illumination of configurations of dots in each 5-dot-wide (46 mm) by 7-dot-high (67 mm) matrix. Actually, only the bottom row of characters is used to present the arithmetic problems. A typical problem might be: 57 + 29 - 45 = ? (answer: 41). The subject enters the answer by using a reverse-order serial entry keyboard; it requires that the least significant digit be entered first. Thus, for the above problem, the subject first enters the number 1, which appears in the extreme right-hand cell of the

bottom row; next, he enters the number 4 and it appears in the cell that is second from the right in that row. Two correction buttons are provided, one for "erasure" of the last digit entered and one for erasing all digits entered. When the subject has entered what he considers to be the correct answer, he depresses a "complete" button. At that time, the accuracy of the answer is determined and, if it is correct, an "R" appears in the cell second from the right of the top row of the display. If the answer is wrong, a "W" appears at that location; simultaneously, the problem and answer are removed from the display. The problem elements in this study could take any value from 11 through 99; they were selected so that neither of the "plus" elements would be the same as the "minus" element and the problems were constructed so that approximately half the answers would be greater than 100 and half less than 100. Time from the introduction of the problem until depression of the complete button is measured in milliseconds. Problems are presented at 20-second intervals.

d. Pattern discrimination. The upper-left six-character by six-row portion of the Burroughs self-scan display is used to present problems on this task. For a given character position in this matrix, all the dots in a 5-dot by 7-dot matrix can be illuminated to form a lighted rectangle. These lighted rectangles are then used to form vertically oriented bargraphs with each column height from one through six appearing just once. The problems on this task are analogous to a question on a multiple-choice examination. The first pattern presented for a given problem is the standard or "question" pattern. This pattern is followed by two comparison patterns that yield three possible answers: (i) one of the comparison patterns might be the same as the standard; (ii) two (both) comparison patterns might be the same as the standard; or (iii) neither comparison pattern might be the same as the standard. The subject indicates his answer by depressing one of three switches labeled "1", "2", and "N." On entering his answer, which is not acknowledged by the system unless made after the onset of the second comparison pattern, the correct answer appears in the extreme upper-left-character position of the display. The timing sequence for this task is as follows: the standard pattern appears for 5 seconds and each comparison pattern appears for 2 seconds with 1 second between patterns; there is a 15-second "off" period after the offset of the second comparison pattern.

Thus, problems are presented every 30 seconds on this task. Both speed of response (measured in milliseconds from the onset of the second comparison pattern) and accuracy are recorded.

e. Problem solving. Each subject's test panel is equipped with five pushbutton switches, a white "task active" light, and three "feedback" lights. The task requires the subject to discover the correct sequence in which to press the buttons in order to turn on a blue feedback light that signifies the problem has been solved. Anytime a button is pushed, an amber light is illuminated to show that the response has been acknowledged by the system. A red light provides error feedback. The subjects are instructed to follow a standard search procedure, always beginning with the leftmost button and proceeding from left to right. The initial illumination of the white and the red lights indicates to the subject that an unsolved problem is present. Subsequently, the red light provides error information as follows: anytime any one of the buttons is depressed, the red light goes out. If the button pushed is the correct first response for a given problem, the red light will remain out when the button is released. Thus, the initial step in solving a problem is to push the buttons one at a time until the button is found that, when released, leaves the red light off. The search then continues for the next button; if it is correct, the red light remains out when that button is released; if it is wrong, the red light comes back on and the button previously determined to be the first button must be pushed again to continue the search for the second button in the sequence. The search proceeds in an analogous manner until each of the five buttons has been pushed just once in the correct sequence for a given problem. At that point, the blue light comes on, signifying that the problem has been solved. After a lapse of 20 seconds, the blue light goes out and the red and white lights come back on; however, this time the onset of those lights indicates that the same problem is being presented a second time. Thus, the subject must remember the correct sequence and cannot (efficiently) solve all problems in a trial-and-error manner without paying attention to which buttons are correct and which are incorrect for a given phase of the solution. After entering the solution a second time and after another lapse of 20 seconds, the blue light goes out and the red and white lights come on, but this time these events signify that a new problem is present.

Thus, efficient performance requires that the subject also remember whether a problem is being presented for the first time or is a repetition of the previous problem. Several measures are derived for this task: (i) the speed of solution of the first presentation of a problem; (ii) the speed of entering the second solution; (iii) the occurrence of redundant responses (responses made when information already acquired should make the subject aware that the response being made is not correct); and (iv) errors made on the second entry of the solution. Although the time between the presentations of problems is fixed at 20 seconds, the rate at which the subject attempts to solve the problem is subject paced; the problem remains until solved.

f. Two-dimensional compensatory tracking. The display for the tracking task is a 7.5-cm oscilloscope cathode ray tube (CRT) mounted in the upper-center part of the subject's panel. The target on the CRT is a dot of light about 1 mm in diameter, and the center of the CRT is defined by horizontal and vertical crosshairs scribed on a plastic cover in front of the CRT. The subject's task is to use a control stick to attempt to counteract a "randomly" varying disturbance imparted to the dot by the computer and keep the dot as near to the intersection of the crosshairs as possible. The maximum amplitude of the disturbance and the stick gain are set so that appropriate manipulation of the stick can always bring the dot to the center of the screen. Performance of the tracking task is scored by analog circuitry that integrates absolute error and a quantity that is proportional to error squared for each dimension. The integration period is 1 minute, and the computer reads out and records the four error measures for each subject at the end of each minute. The error-squared measure is converted to RMS (root mean square) error and, in addition, vector RMS and vector absolute error measures are derived. (Previous research has shown that these measures are all highly intercorrelated; therefore, typically, vector RMS error is used as a single index of tracking performance.)

g. Task combinations. A basic 1-hour schedule of the six tasks was used during both hours of the 2-hour test sessions on the MTPB. The meters and lights monitoring tasks were active throughout the 1-hour schedule. For the first 15 minutes, the arithmetic and tracking tasks were also active. For the second 15 minutes, the arithmetic and the

problem-solving tasks were active. For the third 15 minutes, the pattern discrimination and the problem-solving tasks were active. During the final 15 minutes, the pattern discrimination and tracking tasks were active. There was an approximately 1-minute break between hours and then this same sequence of task combinations was repeated.

4. The Wechsler Memory Scale. This scale consists of seven subtests, the first three of which were not expected to contribute useful data to this study. (Tests 1 and 2 are intended for use with subjects having special defects, such as aphasias. Test 3 consists of counting backwards from 20 to 1, repeating the alphabet, and counting by 3's and 4's).

Test 4, Logical Memory, consists of two memory passages similar to the memory selections on the 10th year of the Stanford-Binet and are similarly scored. The test is intended to measure immediate recall of logical material.

Test 5 is the familiar Memory Span for digits, forward and backward. The series used are those employed in the Wechsler-Bellevue Intelligence Scale except that the maximum number of digits used in the series is limited to eight forward and seven backward.

Test 6, Visual Reproduction, requires the subject to draw simple geometric figures from memory after a 10-second exposure.

Test 7, Associate Learning, consists of 10 paired associates, some easy and some hard; subjects are given three trials and the number of correctly recalled associates is the measure of performance.

The Wechsler Memory Scale comes in two equivalent forms. Form I was administered to each subject for the first drug condition and Form II for the second. Thus, forms were counterbalanced with respect to drug conditions though not with respect to test days. The Wechsler Memory Scale yields a measure that is called the Memory Quotient (MQ). This is the measure that was used in this study and is computed as follows: (i) Sum subject's partial subtest scores. (ii) To this total, which is the subject's raw score, add constant assigned for age group in which subject falls. This new sum is the subject's weighted or corrected memory score.

(iii) Look up the equivalent quotient for this score in a table provided by the test manual. The value found is the subject's MQ as corrected for age.

C. Training. Five subjects in a given group reported to CAMI on Monday, Tuesday, and Wednesday of a test week for training. On Monday morning they were trained on the MTPB in a single 3-hour session. On Tuesday they received an additional 6 hours of training on the MTPB in two 3-hour sessions (0830 to 1130 and 1230 to 1530); at 1530 they received 1 hour of training on the Motor Steadiness Test. On Wednesday they received a 3-hour training session on the MTPB in the morning (0830 to 1130) and a 2-hour session in the afternoon (1230 to 1430). At 1430 they received 1 hour of additional training on the Motor Steadiness Test.

D. Testing. On Thursday of the training week and Monday of the following week, identical schedules were followed except that subjects were given the drug or the placebo in predetermined counterbalanced order. At 0800 the subject was administered two capsules (identical in appearance) that contained either the lactose placebo or the lithium carbonate. The subjects were closely observed from the administration time of the capsules until approximately 0945. This is in excess of the period during which any adverse acute response to the medication would occur; in none of the subjects was there evidence of any adverse response.

From 1000 to 1200 the subjects were tested on the MTPB with an approximately 1-minute break between hours. Between 1215 and 1330 the subjects were tested individually on the Motor Steadiness Test and were given the Wechsler Memory Scale; the first test required about 10 minutes to administer to each subject and the second about 15 minutes. The subjects also ate their lunches during this interval.

At 1400 the subjects were tested for a second 2-hour session on the MTPB, which completed their active testing for the day.

Friday and Tuesday were also characterized by identical schedules. Subjects were aroused at 0630, voided urine, ate breakfast, gave blood samples, and then reported for a 2-hour MTPB test session at 0830. On completion of the MTPB testing

at 1030, the subjects were released (either for the weekend or from the study).

III. Results.

Biomedical measures. Table 1 presents the results of the serum lithium level determinations. Smith, Kline, and French Laboratories report (10) a peak serum lithium level at 2 hours when hourly samples are taken. Apparently, in our study, peaks frequently occurred later. Seven of the fifteen subjects yielded higher values at 4 hours than at 2 hours. Because more frequent sampling was not possible, the time-of-peak and peak values could not be determined. However, from the data obtained, it would appear that most peaks occurred between the 2- and 4-hour samples and were near the 0.5 to 0.6 mEq/liter anticipated for the administered dose.

The findings for the urinary excretion of the 17-ketogenic steroids, epinephrine, and norepinephrine are presented in Figures 3, 4, and 5 respectively. There were no statistically significant differences between placebo and lithium conditions for any of the values. The only significant finding was a difference in the rate of excretion for these hormones for the different collection periods, with the rate being the highest during the first 4-hour collection period and lowest during the overnight period. The level of significance was at the 0.01 level for the 17-ketogenic steroids and at the 0.05 level for the epinephrine and norepinephrine.

The heart rate data are presented in Table 2. In none of the segments were the differences significant.

Motor steadiness. The results of the hand-steadiness test are presented in Table 3. Each score is the sum of the contacts made between the probe and the side of the hole during the two trials when the probe was inserted in the smallest hole. The individual variation for this test is great (scores from 0 to 67 counts). There was no statistically significant difference.

Multiple Task Performance Battery. Performance on the MTPB was assessed by computing a composite score. This score was calculated so that each measure from the individual tasks made an equal contribution to the variance of the composite

TABLE 1. Serum Lithium Levels (mEq/liter)

Subject Number	Time after ingestion (hours)				
	2	4	6	8	24
1	0.05	0.50	0.40	0.30	0.15
2	0.45	0.35	0.30	0.25	0.10
3	0.50	0.40	0.30	0.25	0.10
4	0.35	0.50	0.35	0.30	0.10
5	0.10	0.50	0.40	0.30	0.10
6	0.35	0.35	0.25	0.20	0.10
7	0.45	0.30	0.20	0.15	0.10
8	0.40	0.35	0.30	0.20	0.10
9	0.40	0.50	0.35	0.30	0.15
10	0.35	0.55	0.40	0.30	0.15
11	0.35	0.45	0.40	0.30	0.15
12	0.40	0.30	0.25	0.15	0.10
13	0.50	0.35	0.25	0.20	0.10
14	0.40	0.45	0.35	0.20	0.15
15	0.40	0.35	0.30	0.25	0.10

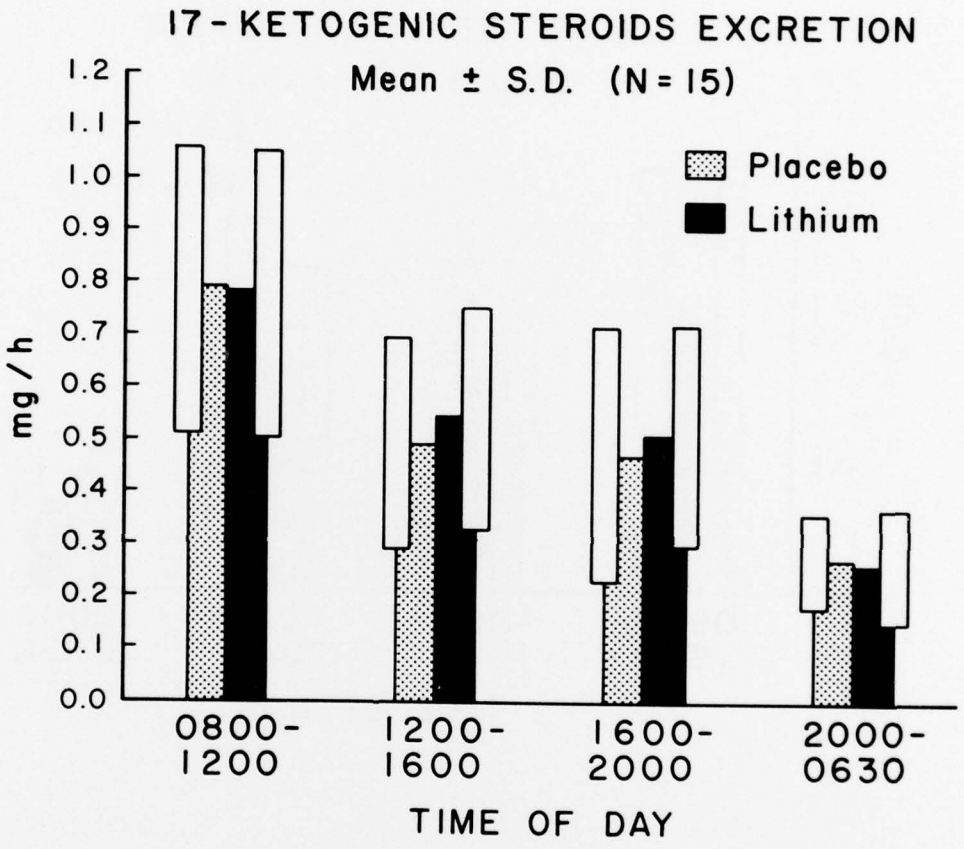

Figure 3. Bargraph of urinary excretion rates of 17-ketogenic steroids.

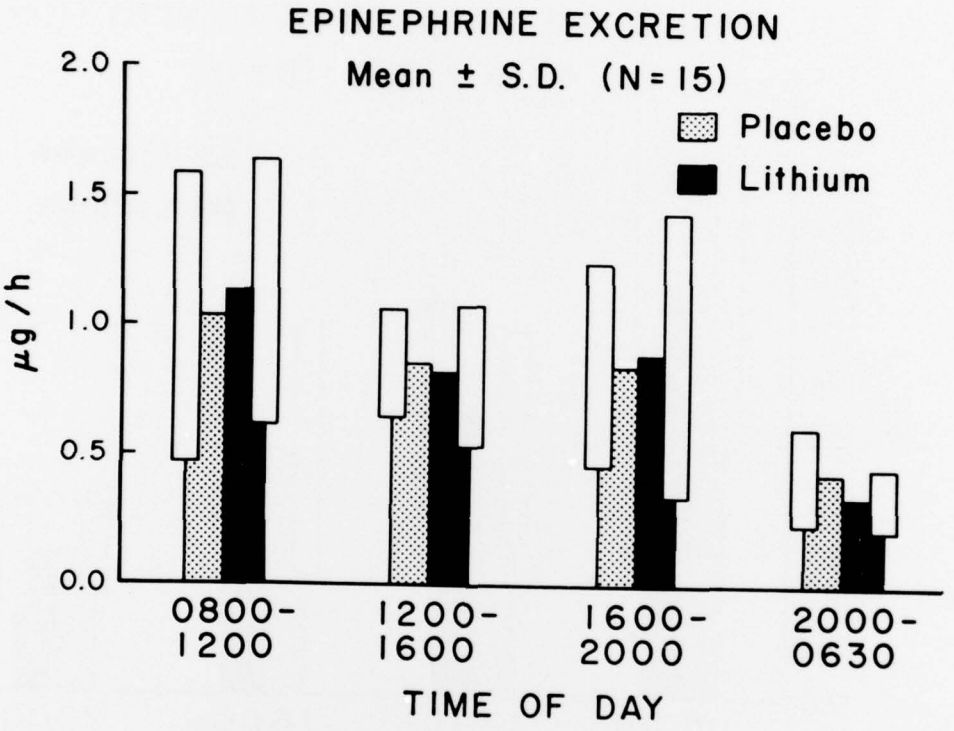

Figure 4. Bargraph of urinary excretion rates of epinephrine.

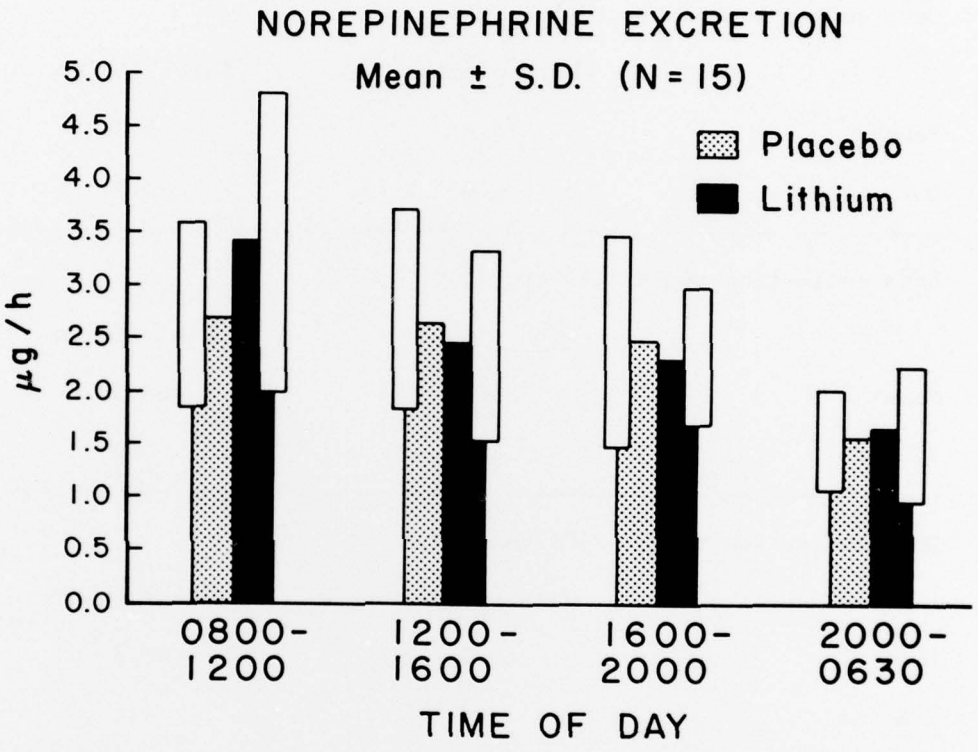

Figure 5. Bargraph of urinary excretion rates of norepinephrine.

TABLE 2. Heart Rate (beats per minute)

Data collection time: 1045 to 1145		
	With placebo	With lithium
Mean*	75.8	75.5
S.D.	4.0	3.7
Data collection time: 1430 to 1530		
	With placebo	With lithium
Mean*	83.5	86.3
S.D.	4.4	4.3
Data collection time: 2400 to 0200		
	With placebo	With lithium
Mean*	60.5	60.3
S.D.	4.0	4.0

* N = 15 Subjects

TABLE 3. Hand-Steadiness Scores

Subject	Placebo	Lithium	d*	Rank of d
1	3.00	13.00	-10.00	- 8
2	11.00	34.00	-23.00	-13
3	8.00	7.00	1.00	1
4	5.00	1.00	4.00	6
5	12.00	22.00	-10.00	- 8
6	1.00	0.00	1.00	1
7	6.00	2.00	4.00	6
8	47.00	18.00	29.00	15
9	31.00	46.00	-15.00	-11
10	24.00	7.00	17.00	12
11	67.00	41.00	26.00	14
12	4.00	2.00	2.00	4
13	19.00	7.00	12.00	10
14	7.00	5.00	2.00	4
15	1.00	0.00	1.00	1
Mean	16.40	13.66		N.S.

* Wilcoxon Matched-Pairs Signed-Rank Test

score; in the case of time scores, reciprocals were used. The resultant measure was then subjected to an analysis of variance in which the main variables were days, drugs, sessions (within days), and hours (within sessions). The only effects that were significant ($p \leq .01$) were days and sessions. In standard score units, day 2 performance was better on the average than day 1 (512.9 vs. 484.0). The standard scores for the three sessions, averaged over days, were 492.7, 490.7, and 512. Although scattered instances of significant drug and drug interaction effects were found for individual task measures, these were inconsistent and hence not interpretable; e.g., a significant decrement for the first 15 minutes but not for the remaining intervals of a session.

The Wechsler Memory Scale. Eight subjects received the lithium first and seven received the placebo first. Table 4 contains the memory quotient scores. Although the two forms of the test that were administered were equivalent forms, there was a significant effect of experience in taking the test ($p \leq .05$), with scores for the second test averaging just over seven MQ points higher. Also, although three individuals scored higher when taking the lithium than when taking the placebo, the average score was significantly ($p \leq .01$) higher when subjects were taking the placebo.

Table 5 lists the results of the paired t test for the seven subtests of the Wechsler Memory Scale. Comparisons were made by using the raw scores. In all seven of the subtests the scores obtained when subjects were taking the placebo were at least slightly higher than when they were taking the lithium. However, subtests 4 and 5 proved to be significantly different and thus made the greatest contribution to the statistical difference reported for the overall MQ score. Subtest 4 is the Logical Memory test and subtest 5 is the Memory Span test.

IV. Discussion.

It has been postulated that depression and mania are caused by alterations in central biogenic amines (4,6,14).

Schildkraut (13), in his review of supporting evidence for "The Catecholamine Hypothesis of Affective Disorders," indicates there is a fairly consistent relationship between

TABLE 4. Memory Quotient Values From Wechsler Memory Scale

Subject number*	Score with lithium	Score with placebo
1	129	135
4	106	94
5	108	116
6	114	110
7	93	105
12	100	112
13	112	132
2	90	110
3	118	112
8	92	94
9	101	129
10	110	146
11	101	118
14	106	129
15	92	137
Mean	104.8	118.6
S.D.	10.9	15.6

* Subjects 1, 4, 5, 6, 7, 12, and 13 received the placebo first. Subjects 2, 3, 8, 9, 10, 11, 14, and 15 received the lithium first.

TABLE 5. Wechsler Memory Scale

Subtest	Mean score (S.D.) lithium	Mean score (S.D.) placebo	t value	Significance* level
1	5.60 (±0.74)	5.93 (±0.26)	-1.58	n.s.
2	4.73 (±0.46)	4.93 (±0.26)	-1.38	n.s.
3	7.87 (±0.83)	8.27 (±0.96)	-1.57	n.s.
4	7.27 (±3.10)	11.13 (±4.16)	-3.68	< 0.01
5	13.20 (±1.21)	14.40 (±0.83)	-4.29	< 0.01
6	12.67 (±1.63)	13.40 (±0.99)	-1.36	n.s.
7	15.67 (±3.18)	16.53 (±0.78)	-0.87	n.s.

* Paired t Test, N = 15

drug effects on catecholamines, especially norepinephrine, and affective or behavioral states. Those drugs that cause depletion and inactivation of norepinephrine centrally produce sedation or depression, while drugs that increase or potentiate brain norepinephrine are associated with behavioral stimulation or excitement and generally exert an antidepressant effect in man. The hypothesis proposes that some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain. Elation, conversely, may be associated with an excess of such amines.

Lithium produces a variety of effects on biogenic amines in animal brains (1,3,16,22). Lithium increases net uptake of amine and increases norepinephrine turnover and deamination (5). Because it is not yet possible to study the function of biogenic amines in the living human brain, inferences must be drawn from animal studies and from human peripheral studies.

In a study reported by Fann et al. (7) in which hypomanic patients were used as subjects, lithium decreased the pressor response produced by norepinephrine by 22 ± 0.6 percent. One study (15) postulates that the long term effects of lithium on norepinephrine turnover are different from the short term effects and that a transient increase in norepinephrine turnover may be observed only during the initial phase of lithium administration.

The finding of no statistically significant difference between placebo and lithium conditions for the urinary excretion of the two catecholamines measured in this study is consistent with other reported studies. The subjects were healthy, and only a single dose of lithium carbonate was administered. Also, the blood-brain barrier restricts the passage of norepinephrine from the brain and, for the most part, this amine must be deaminated before leaving the brain (8). Most urinary norepinephrine, therefore, may be assumed to derive from the peripheral sympathetic nervous system rather than the brain.

In a paper by Platman et al. (12), it is reported that lithium increases the production of cortisol in manic patients. However, this mechanism apparently does not operate in normal

subjects nor in patients during remission. This finding is in agreement with our finding of no significant differences in the 17-ketogenic steroids excreted by the subjects, whether taking lithium or placebo, because our subjects were normal.

Even though fine hand tremor is a common side effect of lithium, it is seldom such a problem as to necessitate the discontinuation of therapy, although it may occasionally require the adjustment of the dose. Schou et al. (20) reported that about 53 percent of patients showed lithium tremor within the first week of treatment. This was not a demonstrable finding in our study. There are several possible reasons. First, our experimental subjects were physically fit, healthy young men. Further, their serum lithium levels were not at the therapeutic levels for which the tremor is more frequently reported. Also, they received only a single dose of lithium carbonate, and no attempt was made to maintain a given serum lithium level.

The significant days effect on the composite score on complex performance could be attributable to learning or to some sort of adaptation to the experimental procedures. The significant sessions effect, with session three performance being better than that of sessions one and two, could have been a result of some sort of placebo effect; e.g., apprehension concerning taking the capsules. However, it is also possible that the controlled activity of the evening plus an insured period of rest were major factors in the higher level of performance during the third session. Unfortunately, neither the days effect nor the sessions effect readily submits to clear interpretation.

There appears to be a significant effect of lithium on short term memory as measured by the Wechsler Memory Scale. It is not, however, a consistent effect, as evidenced by the three subjects who scored higher when taking the lithium than when taking the placebo. Although the differences in placebo scores and lithium scores are less marked for the group that received the placebo first, the apparent discrepancy can be explained by the experience factor in taking the test. There is about a seven-point increase due to experience (Table 6). Group II placebo score minus Group I placebo score is 121.88 - 114.86 = 7.02. Group I lithium score minus Group II lithium score is 108.86 - 101.25 = 7.61. The difference due to the drug effect appears to be about 13 points.

Test I difference between the two groups is 114.86 - 101.25 = 13.61; Test II difference between the two groups is 121.88 - 108.86 = 13.02.

It has been reported that in normal volunteers, lithium caused reduced intellectual initiative, difficulties in comprehending and integrating information about social situations, and feelings of impaired concentration (17,19). In another study using normal volunteer subjects, lithium produced signs of impairment of school performance and work efficiency during the second and third weeks of treatment (21). However, these effects lessened considerably in the fourth week. Perhaps short term memory might follow this same tendency and improve with time of treatment. From our data we can report only the short term effects from a single dose. Also, these were normal subjects for whom there was no apparent indication of a need for the lithium treatment. It would be important to know if the same effect on short term memory would be elicited from those individuals for whom lithium therapy would otherwise be beneficial.

V. Summary.

The effects of a single 600-mg dose of lithium carbonate on short term memory, complex performance, and biomedical functions were assessed in a study of 15 normal, healthy male subjects. The only statistically significant finding due to the lithium carbonate was a decrease in their short term memory as measured by the Wechsler Memory Scale.

TABLE 6. Mean Memory Quotient Scores by Drug and Test Order

	Test I		Test II	
Group I (N = 7)	114.86	P*	108.86	L**
Group II (N = 8)	101.25	L**	121.88	P*

* Placebo
** Lithium

REFERENCES

1. Basuray, B. N., and S. N. Dutta: Effects of Lithium Chloride on Cardiovascular Responses Induced by Cholinergic and Adrenergic Stimulations, EUR. J. PHARMACOL., 28:387-390, 1974.

2. Cade, J. F. J.: Lithium Salts in the Treatment of Psychotic Excitement, MED. J. AUST., 36:349-352, 1949.

3. Corrodi, H., K. Fuxe, T. Hokfelt, and M. Schou: The Effect of Lithium on Cerebral Monoamine Neurons, PSYCHOPHARMACOLOGIA, 11:345-353, 1967.

4. Davis, J. M.: Theories of Biological Etiology of Affective Disorders, INT. REV. NEUROBIOL., 12:145-175, 1970.

5. Davis, J. M., and W. E. Fann: Lithium, ANNU. REV. PHARMACOL., 11:285-303, 1970.

6. Everett, G. M., and J. E. P. Toman: Biological Psychiatry, Proceedings of Scientific Sessions of Society for Biological Psychiatry, San Francisco, 1958, Volume 1, Grune and Stratton, New York, 1959, p. 75.

7. Fann, W. E., J. M. Davis, D. S. Janowsky, J. H. Cavanaugh, J. S. Kaufman, J. D. Griffith, and J. A. Oats: Effects of Lithium on Adrenergic Function in Man, CLIN. PHARMACOL. THER., 13(1):71-77, 1972.

8. Greenspan, K., J. J. Schildkraut, E. K. Gordon, L. Baer, M. S. Aronoff, and J. Durell: Catecholamine Metabolism in Affective Disorders. III, J. PSYCHIATR. RES., 7:171-183, 1970.

9. Hartigan, G. P.: Paper read to the Southern Branch of the Royal Medico-Psychological Society, 1959; reported by Gattozzi, A.: Lithium in the Treatment of Mood Disorders, National Clearinghouse for Mental Health Information, NIMH Publication No. 5033, 1970.

10. Maletzky, B., and P. H. Blachly: The Use of Lithium in Psychiatry, CRC Press, 1971.

11. Melton, C. E., J. M. McKenzie, B. D. Polis, S. M. Hoffmann, and J. T. Saldivar, Jr.: Physiological Responses in Air

Traffic Control Personnel: Houston Intercontinental Tower, FAA Office of Aviation Medicine Report No. AM-73-21, 1973.

12. Platman, S. R., J. G. Hilton, M. C. Koss, and W. G. Kelley: Production of Cortisol in Patients With Manic-Depressive Psychosis Treated With Lithium Carbonate, DIS. NERV. SYST., 32:542-544, 1971.

13. Schildkraut, J. J.: The Catecholamine Hypothesis of Affective Disorders: A Review of Supporting Evidence, AM. J. PSYCHIATRY, 112(1), July-December 1965.

14. Schildkraut, J. J.: Neuropsychopharmacology and the Affective Disorders, Little, Brown and Co., Boston, 1970.

15. Schildkraut, J. J.: The Effects of Lithium on Norepinephrine Turnover and Metabolism: Basic and Clinical Studies, J. NERV. MENT. DIS., 158:348-360, 1974.

16. Schou, M.: Lithium in Psychiatric Therapy: Stock-Taking After Ten Years, PSYCHOPHARMACOLOGIA, 1:65-78, 1959.

17. Schou, M.: Lithium in Psychiatric Therapy and Prophylaxis, J. PSYCHIATR. RES., 6:67-95, 1968.

18. Schou, M.: A Bibliography on the Biology and Pharmacology of Lithium--Appendix I, PSYCHOPHARMACOL. BULL., 8:36-62, 1972.

19. Schou, M., A. Amdisen, and K. Thomsen: The Effect of Lithium on the Normal Mind. In P. Baudis, E. Petrova, and V. Sedivec (Ed.): De Psychiatria Progrediente, Plzen, Vol. 2, pp. 712-721, 1968.

20. Schou, M., P. C. Baastrup, P. Grof, P. Weis, and J. Angst: Pharmacological and Clinical Problems of Lithium Prophylaxis, BR. J. PSYCHIATRY, 116:615-619, 1970.

21. Small, J. G., V. Milstein, H. C. Perez, I. F. Small, and D. F. Moore: EEG and Neurophysiological Studies of Lithium in Normal Volunteers, BIOL. PSYCHIATRY, 5:65-77, 1972.

22. Stern, D. N., R. R. Fieve, N. H. Neff, and E. Gosta: The Effect of Lithium Chloride Administration on Brain and Heart Norepinephrine Turnover Rates, PSYCHOPHARMACOLOGIA 14:315-322, 1969.